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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/884,526	06/19/2001	David Meeker	4274-4000	2532

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EXAMINER	
CHEN, SHIN LIN	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 02/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/884,526	MEEKER ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *2,3 and 7-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 4-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment filed 11-24-03 has been entered. Claims 1 and 4-6 have been amended. Claim 12 has been added. The newly added claim 12 is directed to a combination therapy comprising an enzyme replacement therapy and a small molecule therapy, which is the non-elected invention of group I as indicated in the Official action mailed 11-4-02. Therefore, claim 12 will not be considered by the examiner for the present invention. Claims 1-12 are pending and claims 1 and 4-6 are under consideration.

It should be noted that the elected invention, i.e. a method of combination therapy for treatment of a subject having Fabry disease comprising the combination of gene therapy and enzyme replacement therapy, is under consideration.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 4-6 remain rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MEP. § 2172.01. The omitted steps are: where the enzyme and vector are administered to.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1 and 4-6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants' amendment filed 11-24-03 necessitates this new ground of rejection.

Applicants amended claims 1 and 4-6 to read on administering lysosomal hydrolase and a vector encoding a lysosomal hydrolase to treat Fabry disease. The administration of a lysosomal hydrolase enzyme and a vector encoding a lysosomal hydrolase for treating Fabry disease is considered new matter. The specification states lysosomal storage disease is characterized by a compromised lysosoimal hydrolase (page 1 lines 14, 15) and gene therapy of Fabry disease by using retroviral vector carrying cDNA encoding alpha-Gal A (page 4, lines 24-26). However, there is no nexus between the use of lysosomal hydrolase enzyme and/or a vector expressing a lysosomal hydrolase and the treatment of Fabry disease. The specification only mentions the use of alpha-Gal for treating Fabry disease. Therefore, the specification fails to provide sufficient disclosure for the claimed invention. Thus, administering lysosomal hydrolase and a vector encoding a lysosomal hydrolase to treat Fabry disease is considered new matter.

3. Claims 1 and 4-6 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains,

or with which it is most nearly connected, to make and/or use the invention and is repeated for the reasons set forth in the preceding Official action mailed 5-29-03 (Paper No. 9). Applicant's arguments filed 11-24-03 have been fully considered but they are not persuasive.

Applicants cite Oshima et al., 1997 and US Patent 6,066,626 and argue that animal model for Fabry disease is well-established and gene therapy can restore alpha galactosidase A activity and decrease the accumulation of GL3. Applicants further argue that the specification teaches how to monitor the efficiency of the combination therapy for Fabry disease (amendment, p. 7, 8). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 5-29-03 (Paper No. 9). The existence of animal model for Fabry disease does not warrant successful combination therapy of gene therapy and enzyme replacement therapy for Fabry disease. Although the assay method for monitoring the efficiency of the combination therapy was known in the art, however, the state of the art of gene therapy and enzyme replacement therapy were unpredictable at the time of the invention. US Patent 6,066,626 only reports a method of providing biologically active human alpha-galactosidase A to cells of an individual by administering a vector expressing alpha-galactosidase A to said individual. Delivering a human alpha-galactosidase A to cells of an individual and reduction of GL3 in the cells do not mean that the Gabry disease has been treated. The term "treating" implies that the symptoms of the Fabry disease are ameliorated. The loss of activity of alpha-galactosidase A in Fabry disease patient results in angiokeratomas on the thighs, buttocks, and genitalia, hypohidrosis, cornea verticillata, and clinical manifestations of renal failure, cerebral vascular disease, and myocardial infarction. There is no evidence of record that combination therapy of gene therapy using vector expressing alpha-galactosidase A and enzyme replacement therapy using alpha-galactosidase protein could

provide sufficient alpha-galactosidase A at target cells in vivo so as to ameliorate the symptoms of Fabry disease in a patient.

As discussed in the preceding Official action mailed 5-29-03, the art of gene therapy and enzyme therapy were unpredictable at the time of the invention and the Achilles heel of gene therapy is gene delivery. The fate of the DNA vector itself, the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, the protein's compartmentalization within the cell, or its secretory fate, once produced, and administration route are all important factors for a successful gene transfer. Similarly, the administration route of the protein or enzyme, the amount of the protein or enzyme that reach the target cells, the stability of said protein or enzyme within the cells or during the process of administration, and the protein's compartmentalization within the cell are all important factors for a successful enzyme replacement therapy. The specification fails to provide adequate guidance and evidence for how to use any vector expressing any lysosomal hydrolase, including alpha-galactosidase A, for gene therapy in combination with any lysosomal hydrolase protein, including alpha-galactosidase A, for enzyme replacement therapy to treat Fabry disease in a patient via various administration routes so as to provide therapeutic effects for the Fabry disease *in vivo*.

Applicants argue that the cited reference Deonarain indicates that viral method for gene delivery have been studied for many years, and lauds new improved approach to gene therapy and does not concern unpredictability of gene therapy. Applicants further argue that Verma does

not mention problems with non-viral vectors, AAV vector has been successful in mouse model for hemophilia, and Gorecki does not disclose that gene therapy is unpredictable and suggests that gene therapy holds great promise (amendment, p. 8-10). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 5-29-03 (Paper No. 9) and the reasons set forth above. The claims encompass using various vectors expressing any lysosomal hydrolase via various administration routes. Combination therapy of gene therapy and enzyme replacement therapy has to be considered case by case, a successful gene therapy and enzyme therapy can not be extrapolated into success for another gene and enzyme therapies. Deonarain indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time". Although some vectors might be successful for delivering a particular gene for gene therapy of a particular disease, however, each vector used for gene delivery of a particular gene for gene therapy of a particular disease or disorder must be considered individually because the art of gene therapy and enzyme therapy were unpredictable at the time of the invention. The specification fails to provide sufficient enabling disclosure for the full scope of the invention claimed. Thus, claims 1 and 4-6 remain rejected under 35 U.S.C. 112 first paragraph.

Conclusion

No claim is allowed.

4. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.

SHIN-LIN CHEN
PRIMARY EXAMINER